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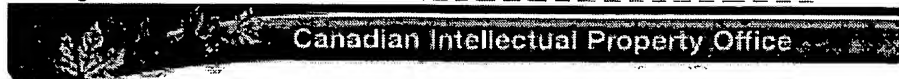
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(11) CA 951661

(54) PROCESS FOR PREPARING SUBSTITUTED PHENYLALKANOIC ACIDS

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### ABSTRACT:

CLAIMS: [Show all claims](#)

\*\*\* Note: Data on abstracts and claims is shown in the official language in which it was submitted.

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**PROCESS FOR PREPARING SUBSTITUTED PHENYLALKANOIC ACIDS**

**Patent number:** CA951661  
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1           This invention relates to novel processes for  
2 preparing L- $\alpha$ -hydrazino- $\beta$ -(3,4-dihydroxyphenyl)propionic  
3 acids.

4           More particularly, this invention relates to pro-  
5 cesses for preparing L- $\alpha$ -hydrazino- $\beta$ -(3,4-dihydroxyphenyl)-  
6 propionic acids by oxidizing L- $\alpha$ -hydrazino- $\beta$ -[3(or 4)-  
7 hydroxyphenyl]propionic acids.

8           It is known in the art that various  $\alpha$ -hydrazino-  
9  $\beta$ -phenylpropionic acids are useful as decarboxylase inhi-  
10 bitors. It is further known that the D-isomer of these  
11 acids is generally inactive and may even be antagonistic to  
12 the action of the L-form, thereby reducing its potency.

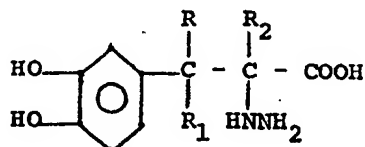
13           In the past, it has been the accepted practice to  
14 separate stereoisomers by the formation of diastereomeric  
15 salts with either optically active bases or acids, depending  
16 on the nature of the racemate. However, with the hydrazino  
17 compounds of the present invention, separation is complicated  
18 by the fact that some diastereomeric salts do not form  
19 crystalline materials with sufficiently different properties  
20 so that the diastereomers can be readily crystallized. In  
21 some instances, the diastereomeric salts are oily or waxy  
22 materials which become difficult if not impossible to sepa-  
23 rate by conventional means. Quite obviously, if a relatively  
24 simple and inexpensive process could be found which would  
25 preferentially produce the desired L- $\alpha$ -hydrazino- $\beta$ -phenyl-  
26 propionic acids, it would receive widespread acceptance in  
27 the art.

28           Accordingly, it is an object of this invention to  
29 provide a process for the preparation of L- $\alpha$ -hydrazino- $\beta$ -  
30 (3,4-dihydroxyphenyl)propionic acids. Other objects of this  
31 invention will become apparent from the ensuing description.



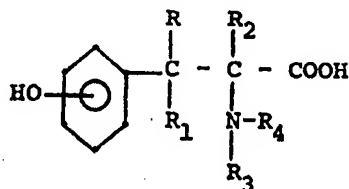
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- 1           These objects are accomplished by the present  
2 invention which provides a process for the preparation of  
3 the L-form of compounds of the formula:



- 4 wherein:

- 5       R, R<sub>1</sub> and R<sub>2</sub> each may be hydrogen or loweralkyl, which  
6 comprises oxidizing the L-form of a compound of the formula:



- 7 wherein:

- 8       R, R<sub>1</sub> and R<sub>2</sub> are as described above;  
9       R<sub>3</sub> is hydrogen or an acyl radical containing less than  
10       about 30 carbon atoms; and  
11       R<sub>4</sub> is NH<sub>2</sub> or N=R<sub>5</sub> wherein R<sub>5</sub> is any divalent radical.  
12       The "loweralkyl" radical signifies an alkyl group  
13       containing from 1 to about 6 carbon atoms which can be  
14       straight chained or branched. The expression "acyl radical"  
15       includes any organic radical derived from an organic acid  
16       by the removal of the hydroxyl group. It includes such  
17       radicals derived from carboxylic acids, sulfonic acids and  
18       the like. Protection of the hydrazino function is optional  
19       during the oxidation process of this invention. Accordingly,  
20       R<sub>4</sub> may be amino or N=R<sub>5</sub> in which case the hydrazino function  
21       is protected by the provision of a divalent radical such as  
22       an imino group, a hydrazone group or a divalent hydrocarbon  
23       radical such as methylene, ethylidene, propylidene, benzyli-  
24       dene, and the like.

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The oxidation reaction of this invention may be carried out by either biological or chemical means. If it is desired to use biological means, fungi such as *Aspergillus ochraceus*, *Gliocladium deliquescens* and *Fusarium solani* are capable of carrying out the required transformation. It will be obvious to those skilled in the art that isolation of the enzyme system decreases the complexity of the medium, decreases the volume of solutions, solvents and reagents, decreases the labor of isolation and increases the efficiency of conversion.

The oxidation may also be accomplished chemically. By illustration L- $\alpha$ -methyltyrosine is converted to L- $\alpha$ -N<sup>1</sup>-acetylhydrazino- $\alpha$ -methyl- $\beta$ -p-hydroxyphenylpropionic acid. This compound is successively nitrated with tetranitromethane, protected, reduced catalytically with hydrogen over platinum the protected amino compound diazotized and with removal of the protective groups L- $\alpha$ -(3,4-dihydroxybenzyl)- $\alpha$ -hydrazino-propionic acid is obtained.

#### EXAMPLE 1

#### 20 L- $\alpha$ -hydrazino- $\alpha$ -methyl- $\beta$ -(3,4-dihydroxyphenyl)propionic acid

L- $\alpha$ -hydrazino- $\alpha$ -methyl- $\beta$ -p-hydroxyphenylpropionic acid (1.98 g., 0.01 mole) is exposed to *Aspergillus ochraceus* in 65 ml. of soybean dextrose medium. L-Ascorbic acid (1.2 g.) is added intermittently over 44 hours in 5 portions. The mixture is acidified with 6 N hydrochloric acid, extracted with n-butanol and the aqueous phase chromatographed on

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Amberlite-IR-120<sup>®</sup> on the acid ( $H_3O^+$ ) cycle. Elution with 1 N ammonium hydroxide yields some unchanged starting material followed by L- $\alpha$ -hydrazino- $\alpha$ -methyl- $\beta$ -(3,4-dihydroxyphenyl)-propionic acid. The product is recrystallized from water containing 0.5% sodium bisulfite to yield product, m.p. 208<sup>o</sup> dec.

EXAMPLE 2L- $\alpha$ -hydrazino- $\alpha$ -methyl- $\beta$ -(3,4-dihydroxyphenyl)propionic acid

10 L- $\alpha$ -methyl-m-tyrosine (97.6 g., 0.5 mole), acetic anhydride (153.1 g., 1.5 moles) and pyridine (200 ml.) are warmed on a water bath at 90-95<sup>o</sup>C. for 3 hours. The mixture is cooled to room temperature, poured onto 500 g. of ice and extracted with ether. The ether extract is washed successively with water, dilute hydrochloric acid and saturated salt solution. After concentration of the mixture *in vacuo* the residue is recrystallized from acetone-hexane to yield L-0,N-diacetyl- $\alpha$ -methyl-m-tyrosine.

20 To a slurry of L-0,N-diacetyl- $\alpha$ -methyl-m-tyrosine (111.7 g., 0.4 mole), water (200 ml.), concentrated hydrochloric acid (56.5 ml.) and 320 ml. of ether is added dropwise at 0-10<sup>o</sup> with vigorous stirring sodium nitrile (29.0 g., 0.42 mole) in water (56.5 ml.). The temperature is maintained at 0-10<sup>o</sup> during the addition and 1 hour additional stirring. The ether layer is separated and the water layer extracted with two 200 ml. portions of ether. The combined

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1 ethereal extract is washed with saturated salt solution  
2 and dried ( $\text{MgSO}_4$ ). The mixture is concentrated in vacuo  
3 to yield L-N,O-diacetyl-N-nitroso- $\alpha$ -methyl-m-tyrosine.

4 A mixture of zinc dust (105 g., 1.6 moles in water  
5 (160 ml.) is stirred and cooled to 10°. The nitroso com-  
6 pound of the previous step in glacial acetic acid (240 ml.)  
7 is added while maintaining the temperature at 10-15°. After  
8 the addition is finished the mixture is allowed to warm to  
9 room temperature over an hour and then warmed to 80° with  
10 stirring on the steam bath. The mixture is filtered to  
11 remove unreacted zinc and the precipitate washed with three  
12 40 ml. portions of warm 2 N hydrochloric acid. The combined  
13 filtrate is cooled to room temperature and with cooling  
14 basified to pH 6.5. The mixture is filtered and the precipi-  
15 tate dried to yield L- $\alpha$ -(N<sup>1</sup>-acetylhydrazino)- $\alpha$ -methyl- $\beta$ -(3-  
16 acetoxyphenyl)propionic acid.

17 The acid from the previous step (103 g., 0.35 mole)  
18 is refluxed with 6 N hydrochloric acid (500 ml.) for 4 hours.  
19 The mixture is concentrated to dryness in vacuo, taken up  
20 in methanol and diethylamine added to pH 6.4. The precipi-  
21 tate is separated by filtration, washed with cold water and  
22 recrystallized from water containing 0.5 sodium bisulfite  
23 to obtain L- $\alpha$ -hydrazino- $\alpha$ -methyl- $\beta$ -(3-hydroxyphenyl)propionic  
24 acid.

25 L- $\alpha$ -hydrazino- $\alpha$ -methyl- $\beta$ -(3-hydroxyphenyl)propionic  
26 acid (2.10 g., 0.01 mole) is exposed to Gliocladium  
27 deliquescens in 65 ml. of soybean dextrose medium. L-ascorbic  
28 acid (1.2 g.) is added intermittently over 44 hours in 5  
29 portions. The mixture is acidified with 6 N hydrochloric

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1 acid, extracted with n-butanol and the aqueous phase chro-  
2 matographed on Amberlite-IR-120<sup>®</sup> on the acid ( $H_3O^+$ ) cycle.  
3 Elution with 1 N ammonium hydroxide yields some starting  
4 material followed by L- $\alpha$ -hydrazino- $\alpha$ -methyl- $\beta$ -(3,4-dihydroxy-  
5 phenyl)propionic acid. The product is recrystallized from  
6 water containing 0.5% sodium bisulfite to yield product,  
7 m.p. 208° dec.

#### 8 EXAMPLE 4

#### 9 L- $\alpha$ -hydrazino- $\beta$ -(3-4-dihydroxyphenyl)propionic acid

10 L-tyrosine (90.6 g., 0.5 mole), acetic anhydride  
11 (153.1 g., 1.5 moles) and pyridine (200 ml.) are warmed on a  
12 water bath at 90-95° for 3 hours. The mixture is cooled to  
13 room temperature, poured onto 500 g. of ice and extracted  
14 with ether. The ether extract is washed successively with  
15 water, dilute hydrochloric acid and saturated salt solu-  
16 tion. After concentration of the mixture in vacuo the  
17 residue is recrystallized from acetone-hexane to yield  
18 L-O,N-diacetyl-p-tyrosine.

19 To a slurry of L-O,N-diacetyl-p-tyrosine (0.4 mole),  
20 water (200 ml.), concentrated hydrochloric acid (56.5 ml.)  
21 and 320 ml. of ether is added dropwise at 0-10° with  
22 vigorous stirring sodium nitrite (29.0 g., 0.42 mole) in  
23 water (56.5 ml.). The temperature is maintained at 0-10°  
24 during the addition and 1 hour additional stirring. The  
25 ether layer is separated and the water layer extracted with  
26 two 200 ml. portions of ether. The combined ethereal  
27 extract is washed with saturated salt solution and dried  
28 ( $MgSO_4$ ). The mixture is concentrated in vacuo to yield  
29 L-N,O-diacetyl-N-nitroso-p-tyrosine.

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1           A mixture of zinc dust (105 g., 1.6 moles) in  
2 water (160 ml.) is stirred and cooled to 10°. The nitroso  
3 compound of the previous step in glacial acetic acid (240 ml.)  
4 is added while maintaining the temperature at 10-15°. After  
5 the addition is finished the mixture is allowed to warm to  
6 room temperature over an hour and then warmed to 80° with  
7 stirring on the steam bath. The mixture is filtered to  
8 remove unreacted zinc and the precipitate washed with three  
9 40 ml. portions of warm 2 N hydrochloric acid. The combined  
10 filtrate is cooled to room temperature and with cooling  
11 basified to pH 6.5. The mixture is filtered and the precipi-  
12 tate dried to yield L- $\alpha$ -(N<sup>1</sup>-acetylhydrazino)- $\beta$ -(4-acetoxy-  
13 phenyl)propionic acid.

14           The acid from the previous step (103 g., 0.35 mole)  
15 is refluxed with 6 N hydrochloric acid (500 ml.) for 4 hours.  
16 The mixture is concentrated to dryness in vacuo, taken up in  
17 methanol and diethylamine added to pH 6.4. The precipitate  
18 is separated by filtration, washed with cold water and recryst-  
19 tallized from water containing 0.5 sodium bisulfite to obtain  
20 L- $\alpha$ -hydrazino- $\beta$ -(4-hydroxyphenyl)propionic acid.

21           L- $\alpha$ -hydrazino- $\beta$ -(4-hydroxyphenyl)propionic acid  
22 (2.10 g., 0.01 mole) is exposed to Gliocladium deliquescens  
23 in 65 ml. of soybean dextrose medium. L-Ascorbic acid (1.2  
24 g.) is added intermittently over 44 hours in 5 portions. The  
25 mixture is acidified with 6 N hydrochloric acid, extracted  
26 with n-butanol and the aqueous phase chromatographed on  
27 Amberlite-IR-120<sup>®</sup> on the acid (H<sub>3</sub>O<sup>+</sup>) cycle. Elution with  
28 1 N ammonium hydroxide yields some starting material followed  
29 by L- $\alpha$ -hydrazino- $\beta$ -(3,4-dihydroxyphenyl)propionic acid. The  
30 product is recrystallized from water containing 0.5% sodium  
31 bisulfite to yield product.

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EXAMPLE 5

1  
2 L- $\alpha$ , $\beta$ -dimethyl- $\beta$ -(3,4-dihydroxyphenyl)- $\alpha$ -hydrazinopropionic  
3 acid

4 A mixture of 3-(p-methoxyphenyl)-2-butanone (314  
5 g., 1.76 moles), potassium cyanide (119.5 g., 1.835 moles),  
6 85% hydrazine hydrate (292 ml.) and water (920 ml.) is stirred  
7 vigorously at room temperature for 30 hours. The product  
8 D,L- $\alpha$ , $\beta$ -dimethyl- $\alpha$ -hydrazino- $\beta$ -(p-methoxyphenyl)propioni-  
9 trile is washed with water and ether and dried. It is not  
10 known whether this product and its derivatives are erythro,  
11 threo or mixed configuration.

12 To a mixture of above hydrazinonitrile (219.3 g.,  
13 1.0 mole) in 2 l. of dioxane and 0.5 l. of tetrahydrofuran  
14 is added simultaneously L-menthoxyacetylchloride (211 g.,  
15 0.95 mole) and triethylamine (133 ml., 0.93 mole). The mix-  
16 ture is stirred at room temperature (25°) overnight. The  
17 precipitated salts and solvents are removed and the residual  
18 oil crystallized from ethyl acetate-hexane. The crystalline  
19 material is crystallized to constant rotation from ethyl-  
20 acetate-hexane to yield L- $\alpha$ , $\beta$ -dimethyl-L-N<sup>2</sup>-(menthoxyacetyl-  
21 hydrazino- $\beta$ -(p-methoxyphenyl)propionitrile.

22 A solution of methanol (50 ml.) and concentrated  
23 hydrochloric acid (60 ml.) is saturated at 0 to -10° with  
24 hydrogen chloride gas. To the mixture at 0° is added with  
25 stirring the above hydrazino-nitrile (8.0 g., 0.0193 mole)  
26 and the stirred mixture is allowed to warm to room tempera-  
27 ture overnight. The solution is concentrated to dryness  
28 in vacuo and the residue dissolved in a mixture of 90 ml.  
29 of concentrated hydrochloric acid and 10 ml. of acetic. The  
30 mixture is heated in an autoclave at 140° for 1.5 hours.

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1           The mixture is cooled and again concentrated to dry-  
2 ness. From the residue refluxing methanol is used to leach  
3 out the hydrazino acid. The volume is concentrated to 50  
4 ml. and after the addition of 10 ml. of benzene, L- $\alpha$ , $\beta$ -di-  
5 methyl- $\alpha$ -hydrazino-p-hydroxyphenylpropionic acid is obtained  
6 by addition of diethylamine to pH 6.5. The product is recryst-  
7 tallized from water containing 0.5% sodium bisulfite and 0.5%  
8 Versene®.

9           The hydrazino acid of the previous steps (2.24 g.,  
10 0.01 mole) is exposed to *Aspergillus ochraceus* in 65 ml. of  
11 soybean dextrose medium. L-Ascorbic acid (1.2 g.) is added  
12 intermittently over 44 hours in 5 portions. The mixture is  
13 acidified with 6 N hydrochloric acid, extracted with n-buta-  
14 nol and the aqueous phase chromatographed on Amberlite-IR-  
15 120® on the ( $H_3O^+$ ) cycle. Elution with 1 N ammonium hydroxide  
16 yields some unchanged starting material followed by L- $\alpha$ , $\beta$ -  
17 dimethyl- $\beta$ -(3,4-dihydroxyphenyl)- $\alpha$ -hydrazinopropionic acid.

18                           EXAMPLE 6

19 L- $\beta$ -(3,4-dihydroxyphenyl)- $\alpha$ -hydrazino- $\alpha$ , $\beta$ , $\beta$ -trimethylpropionic  
20 acid

21           A mixture of 3-(p-methoxyphenyl)-3-methyl-2-buta-  
22 none (384.6 g., 2.0 moles) ammonium carbonate (140.7 g.,  
23 18.2 moles) potassium cyanide (167.5 g., 2.58 moles) water  
24 (5 l.) and ethanol (5 l.) is stirred and heated at 55-60°  
25 for 42 hours. The mixture is cooled to room temperature  
26 (25°) and concentrated in vacuo to 1/2 volume. The product  
27 is filtered, washed, dried and recrystallized from methanol  
28 water to yield D,L-5-( $\alpha$ , $\alpha$ -dimethyl-p-methoxybenzyl-5-methyl-  
29 hydantoin.

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1           To the above hydantoin (262.3 g., 1.0 mole) in  
2 dimethylsulfoxide (2 l.) is added sodium hydride (46.0 g.,  
3 2.0 moles) freed of mineral oil. The mixture is warmed at  
4 50° with stirring until the sodium hydride reacts. The mix-  
5 ture is cooled to room temperature and to it added 2.1 moles  
6 of chloramine in ether. After 1 hour at room temperature the  
7 mixture is warmed to 80° with stirring and stirred at this  
8 temperature for 1 hour. The mixture is concentrated in vacuo  
9 to about 1/4 volume, diluted with an equal volume of water  
10 and filtered. After drying in air at 50° the precipitate  
11 is recrystallized from water to yield D,L-1,3-diamino-5-  
12 ( $\alpha,\alpha$ -dimethyl-p-methoxybenzyl)-5-methylhydantoin.

13           The diaminohydantoin (29.23 g., 0.1 mole) of the  
14 previous step is refluxed with constant boiling hydrobromic  
15 acid (125 ml.) for 3 hours. The mixture is concentrated to  
16 near dryness in vacuo, flushed twice with 50 ml. portions of  
17 t-butanol, extracted with two 100 ml. portions of ethanol and  
18 filtered. After addition of benzene (20 ml.) diethylamine  
19 is added to pH 6.4. The mixture is filtered, the precipi-  
20 tate washed with methanol and dried. The residue is dissolved  
21 in water, treated with charcoal, filtered through diatom-  
22 aceous earth, washed and the product, D,L- $\alpha$ -hydrazino- $\beta$ -  
23 (p-hydroxyphenyl)- $\alpha,\beta,\beta$ -trimethylpropionic acid, recryst-  
24 tallized, filtered, washed and dried.

25           The hydrazino acid (5.09 g., 0.02 mole) is exposed  
26 to *Aspergillus ochraceus* in 130 ml. of soybean dextrose  
27 medium. L-Ascorbic acid (2.0 g.) is added intermittently  
28 over 44 hours in 10 portions. The mixture is extracted with  
29 n-butanol and the aqueous phase chromatographed on Amberlite-  
30 IR-120<sup>®</sup> on the (H<sub>3</sub>O<sup>+</sup>) cycle. Elution with 1 N ammonium  
31 hydroxide yields unchanged D and some L starting material

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1 followed by L- $\beta$ -(3,4-dihydroxyphenyl)- $\alpha$ -hydrazino- $\alpha,\beta,\beta$ ,-tri-  
2 methylpropionic acid. The product is recrystallized from  
3 methanol-water containing 0.5% sodium bisulfite.

4 EXAMPLE 7

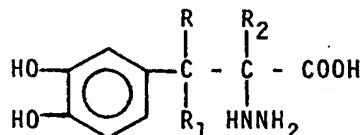
5 L- $\alpha$ -hydrazino- $\alpha$ -ethyl- $\beta$ -(3,4-dihydroxyphenyl)propionic acid

6 L- $\alpha$ -hydrazino- $\alpha$ -ethyl- $\beta$ -p-hydroxyphenylpropionic  
7 acid, (2.23 g., 0.01 mole) is exposed to *Aspergillus ochraceus*  
8 in 65 ml. of soybean dextrose medium. L-Ascorbic acid (1.2 g.)  
9 is added intermittently over 44 hours in 5 portions. The  
10 mixture is acidified with 6 N hydrochloric acid, extracted  
11 with n-butanol and the aqueous phase chromatographed on  
12 Amberlite-IR-120<sup>®</sup> on the acid ( $H_3O^+$ ) cycle. Elution with 1 N  
13 ammonium hydroxide yields some unchanged starting material  
14 followed by L- $\alpha$ -hydrazino- $\alpha$ -ethyl- $\beta$ -(3,4-dihydroxyphenyl)-  
15 propionic acid. The product is recrystallized from water  
16 containing 0.5% sodium bisulfite to yield product.

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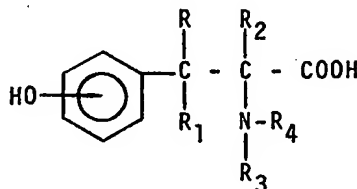
The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A process for the preparation of the L-form of a compound of the formula:



wherein:

R, R<sub>1</sub> and R<sub>2</sub> each may be hydrogen or loweralkyl, which comprises oxidizing in an aqueous medium with a fungal micro-organism selected from *Aspergillus ochraceus*, *Gliocladium deliquescens* and *Fusarium solani* the L-form of a compound of the formula:



wherein:

- R, R<sub>1</sub> and R<sub>2</sub> are as described above;
- R<sub>3</sub> is hydrogen; and
- R<sub>4</sub> is NH<sub>2</sub>, and wherein the hydroxyl group is in the m- or p-position.

2. The process of Claim 1 wherein R is hydrogen, R<sub>1</sub> is hydrogen, R<sub>2</sub> is methyl, R<sub>3</sub> is hydrogen and R<sub>4</sub> is amino.

3. The process of Claim 1 wherein R is methyl, R<sub>1</sub> is hydrogen, R<sub>2</sub> is methyl, R<sub>3</sub> is hydrogen and R<sub>4</sub> is amino.

4. The process of Claim 1 wherein R is hydrogen, R<sub>1</sub> is hydrogen, R<sub>2</sub> is hydrogen, R<sub>3</sub> is hydrogen and R<sub>4</sub> is amino.

ABSTRACT OF THE DISCLOSURE

Process for preparing L- $\alpha$ -hydrazino- $\beta$ -(3,4-dihydroxy-phenyl)propionic acids by the oxidation of L- $\alpha$ -hydrazino- $\beta$ -[3(or 4)-hydroxyphenyl]propionic acid compounds. The oxidation is carried out in an aqueous medium in the presence of a fungal microorganism selected from *Aspergillus ochraceus*, *Gliocladium deliquescens* and *Fusarium solani*.



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